14. (Amended) The method of Claim 28, wherein the outlet has an exposed height of about 0 to 1 mm.

15. (Amended) The method of Claim 28, wherein the outlet has an exposed height of about 0 to 300 μm.

16. (Amended) The method of Claim 28, wherein the delivery rate or volume delivered is controlled by spacing of multiple needles, needle diameter or number of needles.

REMARKS

The undersigned submits herewith an Associate Power of Attorney without revocation or change in mailing address.

Claims 1, 8, and 9 are cancelled without prejudice to the Applicants' right to pursue the subject matter of the canceled claims in one or more related applications. New Claims 25-30 have been added to more particularly point out and distinctly claim the subject matter which the Applicants regard as their invention. After entry of this amendment, Claims 2-7, 10-16, and 25-30 will be pending in the application; for the Examiner's convenience, a copy of the pending claims is provided as Exhibit B. The new Claims 25-30 are fully supported by the instant specification. In particular, support for the claims is provided, *inter alia*, in the specification as described in Table 1 below. Accordingly, no new matter has been added.

TABLE 1: SUPPORT FOR NEW CLAIMS

CLAIM	SUPPORT
25	p.3, lines 32-33; p. 3; lines 13-15; p. 4, lines 29-30; p. 6; lines 11-14; p. 6, lines 21-22
26	p.3, lines 32-33; p. 6, lines 11-14; p. 6, lines 21-29
27	p.3, lines 32-33; p. 5, lines 6-9; p. 6; lines 11-14

28	p.3, lines 32-33; p. 6; lines 11-14
29	p.3, lines 32-33; p. 6; lines 11-14; p. 3; line 35 to p. 4, line 2; p. 6, lines 2-4; p. 7; lines 21-23
30	p.3, lines 32-33; p. 6; lines 11-14; p. 6, lines 2-4; p. 7; lines 21-23; p. 8, lines 8-21; Figures 3 & 4

The Examiner has required the Applicant to submit a drawing of the apparatus under 37 CFR §1.81. However, the Applicants believe that a drawing is not necessary for the understanding of the subject matter sought to be patented, and should not be required. The Applicants respectfully submit that the elected claims are directed to a *method* of delivery of a substance to a human subject, and, as acknowledged by the Examiner, are not limited to the use of any particular device (*see* Office Action at p. 2, discussion of restriction requirement). Thus, the apparatus is not essential to the claimed method, and under 37 CFR §1.81, the Applicants are not required to submit a drawing of a device.

2. <u>The Claimed Invention</u>

The claimed invention relates to delivery of substances to the intradermal compartment of human skin to achieve systemic distribution of that substance in the human body. By way of background, human skin is composed of two major tissue layers, an outer epidermis, and an underlying dermis. The epidermis of human skin is made up of five layers (the outermost impermeable barrier is called the stratum corneum) and has a total thickness of about 75 μm to 150 μm. The dermis lies beneath the epidermis, beginning at a depth of about 60 μm - 120 μm below the skin surface, and is approximately 1-2 mm thick. The dermis contains two layers -- the uppermost portion contains a bed of capillary and lymphatic vessels. The lower layer is relatively avascular, composed of dense connective tissue. Beneath the epidermis and dermis is the subcutaneous tissue, composed of connective tissue and fatty tissue. Muscle tissue lies beneath the subcutaneous tissue.

Systemic distribution of drugs is best achieved by direct injection into a vein, *i.e.*, intravenous (IV) administration. However, IV injections are often impractical, requiring

trained health care specialists for administration. As a result, intramuscular (IM) and subcutaneous (SC) injections (*i.e.*, injections *below* the skin) are the most commonly used routes of administration, even though these modes of administration result in a different pharmacokinetic profile and lower bioavailability (*i.e.*, lower plasma concentration of drug).

The present invention relates to delivering (or targeting) substances to the intradermal compartment of human skin to achieve systemic distribution of the substance in the human body. The space in the intradermal compartment that is targeted in accordance with the invention is close to the capillary bed, allowing for absorption and systemic distribution of the substance, but is above the peripheral nerve net, thereby eliminating or reducing injection pain. The inventors have unexpectedly found that delivery of drugs, for example, to the intradermal compartment results in systemic distribution with a pharmacokinetic profile that is similar to conventional SC administration, but with a much improved bioavailability; *e.g.*, a higher plasma level of circulating drug is achieved in a shorter time period (*see* instant specification at Examples 1 and 2 and Figs. 1-5). Prior to the instant invention, intradermal delivery was rarely used given, in part, the difficulty in maintaining placement of the needle in the intradermal space and overcoming the high backpressure exerted by the skin. However, the inventors have overcome these difficulties, using microneedles of an appropriate length and configuration and controlling the pressure used to discharge the substance.

3. <u>The Claims Are Not Anticipated By Gross or Cirelli</u>

The rejection of the claims as anticipated by Gross (U.S. Patent No. 5,848,991) or Cirelli (U.S. Patent No. 4,886,499) is in error and should be withdrawn. Gross and Cirelli each describe devices which are purported to deliver drugs intradermally. However, a careful review of these references reveals that intradermal delivery and systemic distribution of a drug in human subjects is not, and cannot be achieved using the devices of Gross or Cirelli. Thus, the claims, as amended, are not anticipated.

In particular, the cited references describe devices outfitted with hollow needles having lengths and configurations that will not target the substance to the intradermal compartment of the skin in human subjects. Moreover, the mechanisms for discharging the

drug as described in the cited references result in pressures inadequate to ensure clinically useful systemic distribution of the drug in human subjects. As a result, the method of the invention covered by the amended claims is not described by Gross or Cirelli, and cannot be achieved using the devices of Gross or Cirelli. Therefore, the claims are not anticipated.

2.1. The Claimed Invention Is Not Anticipated by Gross

Claims 1-16 are rejected under 35 U.S.C. §102(e)[1] as anticipated by Gross et al. U.S. Patent No. 5,848,991 ("Gross"). The Examiner contends that Gross discloses a method using small gauge needles to deliver a substance into the intradermal compartment within skin. However, as Applicants discuss below, the amended claims are not anticipated by Gross, and the rejection should be withdrawn.

The devices described in Gross do not have the correct needle length and configuration to deliver a drug to the intradermal compartment of human skin, and achieve systemic distribution of the drug in the human subject, which is the subject matter of the claimed invention. In particular, the range of lengths described by Gross for its single needle delivery devices (*i.e.*, 0.3 mm to 3 mm; *see*, Gross at col. 4, *ll* 10-13) would result in outlet depths that are too shallow at the lower end of the range, or too deep at the higher end of the range to target the intradermal compartment of human skin; and, instead will result in delivery of the drug to the human epidermis or subcutaneous tissue.[2]

The Examiner erroneously contends that Gross discloses an outlet at a depth of about 500 μm to 2 mm for a needle of about 300 μm to 2 mm in length when inserted into the skin

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[1] At p. 4 of the Office Action, Gross is applied against the claims under 35 U.S.C. § 102(e). However, based on its publication date (December 15, 1998), Gross would appear to be available under 35 U.S.C. § 102(b). In either case, Gross does not anticipate the claimed subject matter, and the rejection should be withdrawn for reasons detailed in this response.

[2] By contrast, the Applicants teach administration at a depth of 0.5 mm to 3 mm, preferably about 1 mm to 2 mm into the skin (*See* specification at p. 4, *ll.* 5-7), to achieve intradermal delivery. This can be accomplished using needles no more than 2 mm long and preferably about 0.5 mm to 1 mm long, having outlet depths ranging from 0.25 mm to 2 mm (most preferably 1 mm) when the needle is inserted in the skin (*See* specification at p. 5, *ll.* 9-11).

(Office Action p. 4, citing Gross at col. 3, *ll.* 9-68; col. 4-6, *ll.* 1-68, and col. 7, *ll.* 1-21). If, indeed, Gross contained this disclosure, it would be wrong and nonsensical -- it is physically impossible to have an outlet depth that exceeds the length of the needle! Moreover, a careful reading of the cited sections and the reference as a whole indicates that no disclosure relating to the relative needle length and outlet depth can be found in Gross. It appears that the Examiner, perhaps unwittingly, has attributed disparate teachings from the Applicants' specification into the prior art. This is improper.

Gross is devoid of any teaching relating to the configuration of the needle required to prevent leakage of the drug substance outside the intradermal space. It is the Applicants' disclosure, not Gross, which teaches the importance of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. (*See*, specification at p. 4, *l.* 29 to p. 5, *l.* 21). Unless the skin seals around the needle, the drug substance will effuse out of the skin due to backpressure exerted by the skin itself, or the pressure built up from the accumulating fluid. The Applicants' specification sets forth principles and parameters relating to length of the needle and configuration of its outlet to prevent unwanted leakage. The Applicants' teachings also address mechanisms that can be used to provide adequate pressure so that the drug is efficiently and consistently delivered to the intradermal compartment of human skin where it is readily absorbed and systemically distributed. (For proper needle length and outlet configuration, *see*, instant specification at p. 4, *l.* 29, to p. 5, *l.* 21; for proper pressure requirements to achieve intradermal delivery *see*, instant specification at p. 5, *l.* 22 to p. 6, *l.* 6). In particular, the specification describes the use of microneedles that have *both* a length sufficient to penetrate the intradermal space *and* an *outlet depth within the penetration space* to allow the skin to seal around the needle to prevent effusion of the substance onto the surface of the skin due to backpressure *(See*, specification at p. 5, *ll.* 6-10). Gross neither appreciates nor addresses the significance of these parameters for practicing the claimed method.

Gross also fails to appreciate the complications associated with true intradermal delivery in human subjects, such as those resulting from backpressure exerted by the skin itself and the pressure built up from accumulating fluid. This failure may be attributable to

Gross's use of an inappropriate animal model (*e.g.*, a rabbit as demonstrated in Example 1 of Gross at col. 10, *ll.* 33 to 45) in which the skin thickness does not provide the correct approximation to that of human skin. (*See*, Corbo *et al.*, 1989, *Pharmaceutical Research*, 6(9): 753-8, submitted herewith). The prototype model for human skin, as acknowledged by those skilled in the art, is pig since the thickness of the pig's various skin compartments most closely approximates human skin. (*See,* Bronaugh *et al.*, 1982, *Toxicology & Applied Pharmacology*, 62:481-8, also submitted herewith). The pig model is precisely the one used by Applicants (*See* specification at Examples 1 and 2).

Thus, in view of the foregoing, Gross cannot anticipate the claimed invention.

2.2. <u>The Claimed Invention Is Not Anticipated by Cirelli</u>

Claims 1-5 and 8-16 are rejected under 35 U.S.C. §102(b) as anticipated by Cirelli et al. U.S. Patent No. 4,886,499 ("Cirelli"). The Examiner erroneously contends that Cirelli discloses a method using small gauge needles to deliver a substance into the intradermal compartment of the skin. However, the needle used in Cirelli's drug delivery device does not have the correct length to penetrate into the intradermal compartment of the skin. Specifically, the needles of Cirelli's device range from 50 μm to 5000 μm in length (Cirelli at col. 3, *ll* 8-15) and penetrate the skin "something like at least 50 μm, and at most approximately 5000 μm" (Cirelli at col. 5, *ll.* 9-11). The lower limit of the range specified (0.05 mm) simply penetrates the epidermis, and the upper limit of the range (5 mm) goes beyond the intradermal compartment and rather, penetrates the subcutaneous compartment of the skin. Therefore, Cirelli does not anticipate the claimed invention.

Moreover, the Examiner erroneously contends that Cirelli discloses an outlet at a depth of about 500 μm to 2 mm, a needle length of about 300 μm to 2 mm, and refers to col. 3, *ll.* 45-68; cols. 4-6, *ll.* 1-68, col. 7, *ll.* 1-20). This disclosure, if it existed in Cirelli, as previously explained, is incorrect. Moreover, a careful reading of the cited sections as well as the reference as a whole indicates no such disclosure relating to relative needle lengths and outlet depths. Again, Applicants respectfully submit that it is both incorrect and improper to read disparate portions of the applicant's own teachings into the prior art for purposes of anticipation.

In view of the foregoing, Cirelli cannot anticipate the claimed invention.

2. The Claimed Invention Is Not Made Obvious By Cirelli Combined With Cheikh

The rejection of the claims as made obvious over Cirelli (U.S. Patent No. 4,886,499) in view of Cheikh (U.S. Patent No. 5,582,591) is in error and should be withdrawn.[3] A careful review of these references reveals that intradermal delivery and systemic distribution of a drug in a human subject is not suggested nor made obvious by the references, taken alone or in combination.

The Examiner contends that the use of a needle as taught by Cirelli combined with the administration of PTH and insulin as taught by Cheikh makes obvious the claimed invention. This rejection is in error and should be withdrawn.

As discussed above, the needle used in the drug delivery device described in Cirelli does not have the correct length or configuration to target a drug to the intradermal compartment of human skin so that systemic distribution is achieved, which is the subject mater of the claimed invention. This deficiency is not cured by combining Cirelli with Cheikh. The delivery devices described in Cheikh employ a hollow needle of unspecified length, thus Cheikh does not even provide a suggestion of an appropriate range of needle lengths (much less configuration of the outlet) to target a substance to the intradermal compartment of human skin so that painless systemic distribution is achieved.

Thus, the combination of Cirelli and Cheikh does not arrive at a suggestion of a successful way to deliver a substance to the intradermal compartment of human skin to achieve systemic distribution. Therefore, the rejections in view of Cirelli and Cheikh should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal

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[3] On p. 6 of the Office Action, the Examiner variably refers to Cheikh and Stout. Since the cites given do not correspond to Stout, but do appear to correspond to Cheikh we are addressing the rejection of the claims based on the combination of Cirelli with Cheikh.

of all rejections, and an early allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

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